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Antistaphylococcal penicillins versus cephalosporins for definitive treatment of meticillin-susceptible *Staphylococcus aureus* bacteraemia: A systematic review and meta-analysis

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ABSTRACT

The objective of this study was to assess the comparative effectiveness and safety of antistaphylococcal penicillins (ASPs) and cephalosporins for the definitive treatment of patients with meticillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia. PubMed and Scopus electronic databases were searched up to December 2013. All-cause mortality was the primary outcome of interest. A meta-analysis of unadjusted and adjusted data was performed. Seven articles (1643 patients) were included; all but one were retrospective studies, and three of them employed propensity score matching. The studies enrolled primarily adults hospitalised in medical wards for primary or secondary community-acquired, healthcare-associated or nosocomial MSSA bacteraemia. Several ASPs and cephalosporins were compared. Unadjusted 30-day mortality was lower in patients treated with ASPs than in those treated with cephalosporins [risk ratio (RR) = 0.62, 95% confidence interval (CI) 0.40–0.98]. Propensity score-adjusted 30-day mortality was not different in patients receiving ASPs or cephalosporins (RR = 0.75, 95% CI 0.41–1.39). Substantial heterogeneity and publication bias were found in these analyses. Both unadjusted (RR = 0.85, 95% CI 0.54–1.32) and adjusted (RR = 1.42, 95% CI 0.22–9.06) 90-day mortality did not differ between patients receiving ASPs or cephalosporins. Limited data regarding adverse events, development of resistance and recurrence were available. In conclusion, the limited available published data derive from retrospective studies and show that there appears to be no statistically significant difference in mortality between ASPs and cephalosporins for the treatment of MSSA bacteraemia.

1. Introduction

Studies performed worldwide have shown that *Staphylococcus aureus* is among the leading pathogens causing bacteraemia [1–3]. The incidence both of hospital- and community-acquired *S. aureus* bacteraemia (SAB) has risen during the past decades owing to frequent use of intravascular devices, larger numbers of immunocompromised patients and an increased number of surgical procedures [1–3]. Despite improvements in healthcare services and antimicrobial drug treatment, mortality rates remain high. In particular, it has been estimated that the death rate for infections due to meticillin-resistant *S. aureus* (MRSA) is 34.2%, whilst that for meticillin-susceptible *S. aureus* (MSSA) is 25% [4].

Although SAB remains a common infection associated with significant morbidity and mortality, limited clinical data exist for optimal antibiotic therapy, especially regarding MSSA bacteraemia. Historically, antistaphylococcal penicillins (ASPs), e.g. oxacillin, nafcillin, cloxacillin, dicloxacillin and flucloxacillin, were considered to be the treatment of choice for SAB caused by penicillin-resistant strains, whilst cephalosporins were considered an alternative option. However, the comparative clinical effectiveness of β-lactams against MSSA bacteraemia has not been clearly estimated.

In the absence of randomised controlled trials (efficacy studies), the selection of antimicrobial agents for MSSA bacteraemia was based on local availability of antibiotics, clinical experience and *in vitro* studies. Experimental studies indicated that ASPs are superior to cephalosporins and are more bactericidal [5,6]. Recently, experimental studies demonstrated the high inoculum effect among

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clinical isolates of MSSA with cefazolin treatment, suggesting a possible cause of cefazolin treatment failure reported in case reports and animal models [5,7]. To our knowledge, few studies that assessed the comparative effectiveness and safety of β-lactams for the treatment of MSSA bacteraemia have been published. Hence, in this systematic review, we evaluated the effectiveness and safety of ASPs compared with cephalosporins.

2. Methods

2.1. Literature search

With the aim of collecting data about the treatment of MSSA bacteraemia, a search of the literature was performed using the Scopus and PubMed electronic databases up to December 2013. A review protocol was not done. Two of the authors (KZV and KNA) searched the literature independently. The search term applied in both databases was: '(*staphylococcus aureus*) AND (meticillin-sensitive OR meticillin-susceptible OR MSSA) AND (bacteremia OR septicemia OR blood stream infection)'. Any article written in English and providing comparative data for patients treated with either ASPs or cephalosporins for MSSA bacteraemia was considered eligible. Reference lists of included studies and relevant reviews were screened for further potentially eligible publications. Studies that were presented as abstracts at scientific conferences but have not been published were not evaluated. The corresponding authors of articles were contacted via e-mail if the required data were not available in the publications.

2.2. Inclusion and exclusion criteria

Studies of interest were those reporting crude outcomes or assessing penicillins or cephalosporins as predictors for clinical outcomes of patients with primary or secondary bacteraemia caused only by MSSA; those investigating patients with staphylococcal infections without bacteraemia were excluded. In addition, articles reporting outcomes on resistant strains such as MRSA or vancomycin-intermediate *S. aureus* (VISA) were not included. Studies of any design besides case reports, small case series up to 10 patients, and cohorts of patients receiving only either ASPs or cephalosporins were excluded. Both observational and interventional studies performed on humans could be included. Articles referring to experimental animal models and microbiological activity of antibiotics were omitted. Studies enrolling patients of any age were eligible for inclusion. The population of the selected studies could have received any penicillin with antistaphylococcal activity as well as first-, second- and third-generation cephalosporins. Both monotherapy and combination antibiotic regimens (containing other non-β-lactam antibiotics) could be analysed if the additional antibiotics were evenly distributed between the compared groups. Studies on patients receiving outpatient antibiotic treatment were not evaluated. There was no screening for the source of bacteraemia, implying that it could be hospital-acquired, community-acquired or healthcare-associated.

2.3. Extracted data, definitions and outcomes

Data regarding the characteristics of the study (author, study design, period, location, number of enrolled patients) and the patients (age, sex, site and source of infection, antibiotics administered in each group) were extracted. Mortality, duration of intravenous treatment and hospitalisation, recurrence of bacteraemia, and adverse events leading or not to the discontinuation of antimicrobial treatment were also recorded. Data were extracted independently by two authors (KZV and KNA). Discrepancies were resolved in meetings between the two authors.

The primary outcome of the meta-analysis was all-cause mortality (preferably at 30 days) among patients treated definitively with a β-lactam antibiotic (combination or monotherapy). If data at different time points were provided in the individual studies, a separate analysis according to these time points was performed. Both unadjusted and adjusted mortality were recorded, considering the second one more clinically important. Infection-related mortality, recurrence of bacteraemia, adverse events due to antimicrobial treatment, and emergence of resistance were defined as secondary outcomes.

The definition of bacteraemia and bacteraemia acquisition source was based on the definitions provided by the individual studies. In particular, diagnosis of bacteraemia depended on the growth of MSSA at least in two separate sets of blood cultures with or without the presence of systemic inflammatory response syndrome within 48 h of a positive blood culture with no other source of infection. Hospital-acquired bacteraemia was defined as a positive blood culture obtained >48 h after hospital admission, and community-onset bacteraemia was defined as a positive blood culture obtained within 48 h of admission. Patients who had been hospitalised within 90 days prior to the MSSA bacteraemia or visited the hospital regularly (e.g. for chemotherapy or haemodialysis) or were residents of chronic healthcare facilities or nursing homes were considered to have healthcare-associated bacteraemia. As far as the antibiotic regimen is concerned, treatment given to the patient after the blood culture results were available was defined as definitive treatment.

2.4. Statistical analysis

The meta-analysis was performed with Review Manager for Windows v.5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration. Copenhagen, Denmark). Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated regarding all adjusted and unadjusted outcomes. Statistical heterogeneity among studies was assessed by χ^2 test ($P < 0.10$ was defined to indicate significant heterogeneity) and I^2. The Mantel–Haenszel fixed-effect model was used when there was no significant statistical heterogeneity between the studies; otherwise, the random-effects model was used as appropriate. Pre-specified subgroup analyses were performed for unadjusted and adjusted data, primary or secondary bacteraemia, site of bacteraemia onset/acquisition, specific penicillins or cephalosporins, and patients treated with combination of antibiotics.

3. Results

Fig. 1 summarises the selection process of articles eligible for inclusion in the systematic review and meta-analysis. After a thorough search of electronic databases, 575 and 476 articles were identified and screened in PubMed and Scopus, respectively, from which 44 full-text articles were assessed for eligibility, among which 7 were selected for the meta-analysis [8–14]. The rest of the retrieved studies were excluded because of ineligible outcomes. The different reasons that led to their exclusion are shown in Fig. 1. The first or corresponding author of three of the included studies was contacted via e-mail. All of them sent the requested data [8–10].

Table 1 shows the characteristics of the included studies. The selected articles were cohort studies conducted from 1988 onwards. The majority of the studies were retrospective (one was prospective) and three of them employed propensity score matching. Treatment and outcome data for 1643 patients with MSSA bacteraemia were available. Almost all of them were adults (aged ≥16 years); the mean age varied from 45 years to 70 years. The